

Modeling disease in human embryonic stem cells using new genetic tools

Grant Award Details

Modeling disease in human embryonic stem cells using new genetic tools

Grant Type: Basic Biology IV

Grant Number: RB4-05855

Project Objective: The goal of this grant is to model disease in hESC using the floxin system, a versatile genetic tool the PI has successfully developed for use in mESC and that will now be adopted for use in hESC. Genes will be trapped using gene trap vectors with strong splice acceptors and otherwise designed to allow cre-mediated insertion of sequences into the trapped locus. Typically, trapped loci display loss of function, and insertion of sequences can restore gene function by introduction of cDNAs expressing the disrupted gene. Alternatively, disease alleles of the gene, as well as tagged versions, or reporter genes can be introduced. In each case, the introduced sequences will be under the control of the endogenous locus. This grant will establish the floxin system for use in hESC, and generate ~ 1000 gene trap hESC lines and a floxin tool kit for use by the research community. Per Amendment Number 02 Dated 08/7/14

The originally proposed aim of generating a library of gene trapped hESC lines has been superseded by the development of the CRISPR/Cas9 system for targeting genome manipulations. The PI will instead assess the efficacy of the combined CRISPR/Piggy/Bac/Floxin system, assess whether it can generate homozygous targeted insertions, and assess whether the system can efficiently generate tagged alleles, point alleles, Cre insertions and other bespoke alleles.

Investigator:

Name: Jeremy Reiter

Institution: University of California, San Francisco

Type: PI

Disease Focus: Neurological Disorders, Neuropathy

Human Stem Cell Use: Embryonic Stem Cell

Award Value: \$1,387,800

Status: Closed

Progress Reports

Reporting Period: Year 1

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| Reporting Period: | Year 2 |
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| Reporting Period: | Year 3 |
| View Report | |

Grant Application Details

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| Application Title: | Modeling disease in human embryonic stem cells using new genetic tools |
| Public Abstract: | <p>The use of stem cells or stem cell-derived cells to treat disease is one important goal of stem cell research. A second, important use for stem cells is the creation of cellular models of human development and disease, critical for uncovering the molecular roots of illness and testing new drugs. However, a major limitation in achieving these goals is the difficulty in manipulating human stem cells. Existing means of generating genetically modified stem cells are not ideal, as they do not preserve the normal gene regulation, are inefficient, and do not permit removal of foreign genes.</p> <p>We have developed a method of genetically modifying mouse embryonic stem cells that is more efficient than traditional methods. We are adapting this approach for use with human embryonic stem cells, so that these cells can be better understood and harnessed for modeling, or even treating, human diseases. We will use this approach to create a human stem cell model of Charcot-Marie-Tooth (CMT) disease, an inherited neuropathy. How gene dysfunction leads to nerve defects in CMT is not clear, and there is no cure or specific therapy for this neurological disease. Thus, we will use our genetic tools to investigate how gene function is disrupted to cause CMT. By developing these tools and using them to gain understanding of CMT, we will illustrate how this system can be used to gain insight into other important diseases.</p> |
| Statement of Benefit to California: | <p>Although human stem cells hold the potential to generate new understanding about human biology and new approaches to important diseases, the inability to efficiently and specifically modify stem cells currently limits the pace of research. Also, there is presently no safe means of changing genes compatible with the use of the stem cells in therapies. We are developing new genetic tools to allow for the tractable manipulation of human stem cells. By accelerating diverse other stem cell research projects, these tools will enhance the scientific and economic development of California.</p> <p>We will use these tools to create cellular models of Charcot-Marie-Tooth (CMT), a neurological disease with no cure that affects about 15,000 Californians. This model will facilitate understanding of the etiology of CMT, and may lead to insights that can be used to develop specific therapies.</p> <p>Beyond gaining insight into CMT, the ability to engineer specific genetic changes in human stem cells will be useful for many applications, including the creation of replacement cells for personalized therapies, reporter lines for stem cell-based drug screens, and models of other diseases. Thus, our research will assist the endeavors of the stem cell community in both the public and private arenas, contributing to economic growth and new product development. This project will also train students and postdoctoral scholars in human stem cell biology, who will contribute to the economic capacity of California.</p> |

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